WEST

☐ Generate Collection Print

L2: Entry 3 of 7 File: USPT Oct 30, 2001

US-PAT-NO: 6309633
DOCUMENT-IDENTIFIER: US 6309633 B1

TITLE: Amphiphilic drug-oligomer conjugates with hydroyzable lipophile components and methods for making and using the same

DATE-ISSUED: October 30, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ekwuribe; Nnochiri	Cary	NC		
Ramaswamy; Muthukumar	Cary	NC		
Rajagopalan; Jayanthi Sethuraman	Cary	NC		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Nobex Corporation	Research Triangle Park	NC			02

APPL-NO: 09/ 336548 [PALM]
DATE FILED: June 19, 1999

INT-CL: [07] A61 K 9/107, A61 K 38/17, A61 K 38/28, A61 K 39/385, C07 K 1/113

US-CL-ISSUED: 424/85.1; 424/85.2, 424/85.4, 424/94.3, 424/193.1, 424/194.1, 435/188, 514/2, 514/3, 514/8, 514/12, 514/21, 514/476, 514/506, 514/579, 514/613, 514/715, 530/303, 530/345, 530/405, 530/406, 530/409, 530/410 , 530/411
US-CL-CURRENT: 424/85.1; 424/193.1, 424/194.1, 424/85.2, 424/85.4, 424/94.3, 435/188, 514/12, 514/2, 514/21, 514/3, 514/476, 514/506, 514/579, 514/613, 514/715, 514/8, 530/303, 530/345, 530/405, 530/406, 530/409, 530/410 , 530/411

FIELD-OF-SEARCH: 424/85.1, 424/85.2, 424/85.4, 424/85.5, 424/85.6, 424/85.7, 424/94.3, 424/178.1, 424/179.1, 424/193.1, 424/194.1, 435/188, 514/2, 514/3, 514/8, 514/12, 514/21, 514/476, 514/506, 514/579, 514/613, 514/715, 530/300, 530/303, 530/322, 530/345, 530/350, 530/351, 530/403, 530/405, 530/406, 530/409, 530/410, 530/411

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	3256153	June 1966	Heimlich	424/477
☐	3868356	February 1975	Smyth	530/303
☐	4003792	January 1977	Mill et al.	530/303
☐	4044196	August 1977	Huper et al.	526/271
☐	4087390	May 1978	Shields	525/54.11
☐	4093574	June 1978	Shields	525/54.11
☐	4100117	July 1978	Shields	525/54.11
☐	4179337	December 1979	Davis et al.	435/181
☐	4229438	October 1980	Fujino et al.	514/15
☐	4253998	March 1981	Sarantakis	525/54.11
☐	4277394	July 1981	Fujino et al.	530/330
☐	4410547	October 1983	Ueno et al.	514/557
☐	4585754	April 1986	Meisner et al.	514/8
☐	4622392	November 1986	Hong et al.	536/29
☐	4684524	August 1987	Eckenhoff et al.	424/469
☐	4698264	October 1987	Steinke	428/402.2
☐	4717566	January 1988	Eckenhoff et al.	424/438
☐	4744976	May 1988	Snipes et al.	424/408
☐	4772471	September 1988	Vanlerberghe et al.	424/450
☐	4797288	January 1989	Sharma et al.	424/476
☐	4840799	June 1989	Appelgren et al.	424/493
☐	4849405	July 1989	Ecanow	514/3
☐	4935246	June 1990	Ahrens	424/490
☐	4946828	August 1990	Markussen	514/3
☐	4963367	October 1990	Ecanow	424/485
☐	5013556	May 1991	Woodle et al.	424/450

☐	5055300	October 1991	Gupta	424/409
☐	5055304	October 1991	Makino	424/465
☐	5093198	March 1992	Speaker et al.	428/402.21
☐	5164366	November 1992	Balschmidt et al.	514/3
☐	5359030	October 1994	Ekwuribe	530/303
☐	5438040	August 1995	Ekwuribe	514/3
☐	5545618	August 1996	Buckley et al.	514/12
☐	5606038	February 1997	Regen	536/6.5
☐	5681567	October 1997	Martinez et al.	424/178.1
☐	5681811	October 1997	Ekwuribe	514/8
☐	5693609	December 1997	Martinez et al.	514/3
☐	5693769	December 1997	Kahne et al.	536/5
☐	5824638	October 1998	Burnside et al.	514/3
☐	5830918	November 1998	Sportsman et al.	514/648
☐	5907030	May 1999	Shen et al.	530/331
☐	5932462	August 1999	Harris et al.	435/188

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
31567	August 1981	EP	
95/09831	April 1995	WO	
95/30641	November 1995	WO	
98/07745	February 1998	WO	

OTHER PUBLICATIONS

King et al. Preparation of Protein Conjugates Within Int. J. Pept. Prot. Res. vol. 16, pp. 147-155, 1980.*
International Search Report, PCT/US00/16879, Aug. 23, 2000.
Delgado et al. "The Uses and Properties of PEG-Linked Proteins". Critical Review in Therapeutic Drug Carrier Systems, 9(3, 4):249-304 (1992).
Aoshima, M. et al., "N.sub.4 -Behenoyl-1-.beta.-D-Arabinofuranofuranosylcytosine as a Potential New Antitumor Agent," Cancer Research 1977, 37; pp. 2481-2486.
Baker, D.C. et al., "Prodrugs of 9-.beta.-D-Arabinofuranosyladenine. 1. Synthesis and Evaluation of Some 5'-(O-Acyl) Derivatives," J. Med. Chem., 1978, 21(12); pp. 1218-1221.
Banting, R. G. et al, "Pancreatic Extracts in the Treatment of Diabetes Mellitus," The Canadian Med. Assoc. J. 1922, 12:141-146.

Boccu, E. et al., "Pharmacokinetic Properties of Polyethylene Glycol Derivatized Superoxide Dismutase," Pharm. Res. Comm., 1982 14:11-120.
Brange, J. et al, "Chemical Stability of Insulin. 1. Hydrolytic Degradation During Storage of Pharmaceutical Preparations," Pharm. Res., 1992, 9 (6): 715-726.
Brange, J. et al, "Chemical Stability of Insulin. 2. Formation of Higher Molecular Weight Transformation Products During Storage of Pharmaceutical Preparations," Pharm. Res., 1992, 9 (6) 727-734.
Conradi, R. A., et al., "The Influence of Peptide Structure on Transport Across Caco-2 Cells," Pharm. Res., 1991, 8 (12):1453-1459.
Gish, D. T. et al., "Nucleic Acids. 11. Synthesis of 5'-Esters of 1-beta -D-Arabinofuranosylcytosine Possessing Antileukemic and Immunosuppressive Activity," J. Med. Chem., 1971, 14(12): pp. 1159-1162.
Hong, C. I. et al., "Nucleoside Conjugates. 7. Synthesis and Antitumor Avitvity of 1-beta -D-Arabinofuranosylcytosine Conjugates of Ether Lipids," J. Med. Chem., 1986, 29: pp. 2038-2044.
Hostetler, K. Y. et al., "Synthesis and Antiretroviral Activity of Phospholipid Analogs of Azidothymidine and Other Antiviral Nucleosides," The Journal of Biological Chemistry, 1990, 265(11): pp. 6112-6117.
M. Maislos et al, "The Source of the Circulating Aggregate of Insulin in Type 1 Diabetic Patients is Therapeutic Insulin" J. Clin. Invest., 1986, 77:717-723.
Oka, K. et al, "Enhanced Intestinal Absorption of a Hydrophobic Polymer-conjugated Protein Drug, Smancs, in an Oily Formulation" Pharm. Res., 1990, 7 (8): 852-855.
Ratner, R. E. et al, "Persistent Cutaneous Insulin Allergy Resulting from High-Molecular Weight Insulin Aggregates." Diabetes, 1990, 39:728-733.
Robbins et al, "Antibodies to Covalent Aggregates of Insulin . . . ", Diabetes, 1987, 36:838-841.
Saffran et al. "A Model for the Study of the Oral Administration of Peptide Hormones" Can J Biochem 57 548-553 1979.
Saffran, M. et al, "A New Approach to the Oral Administration of Insulin and Other Peptide Drugs," Science, 1986, 233:1081-1084.
Shichiri, Y. et al., "Enteral absorption of water-in-oil-in-water insulin emulsions and rabbits," Diabetologia, 10:317-321 (1974).
Engel, S., et al., "Insulin: intestinal absorption as water-in-will-in-water emulsions," Nature, 219:856-857 (1968).
JC Price, "Polyethylene Glycol," pp. 355-361 (Not dated).
Fasano, A., "Innovative strategies for the oral delivery of drugs and peptides," TIBTECH. Apr. 1998. vol. 16, pp. 152-157.

ART-UNIT: 163

PRIMARY-EXAMINER: Russel; Jeffrey E.

ATTY-AGENT-FIRM: Myers Bigel Sibley & Sajovec, P.A.

ABSTRACT:

The invention provides a drug-oligomer conjugate having the following general formula: ##STR1##

wherein D is a therapeutic drug moiety; H and H' are each a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars; L is a lipophilic moiety selected from the group consisting of alkyl groups having 2-26 carbon atoms, cholesterol, adamantane and fatty acids; o is a number from 1 to the maximum number of covalent bonding sites on H; m+n+p together have a value of at least one and not exceeding the total number of covalent bonding sites on D for the --H', --L and --H--L substituents; the H--L bond(s) are hydrolyzable and the D--L' bond(s), when

present, are hydrolyzable; the conjugate being further characterized by one of the following: (i) m is 0 and p is at least 1; (ii) n is 0 and p is at least 1; (iii) m and n are each 0 and p is at least 1; (iv) p is 0 and m and n are each at least 1. The therapeutic drug moiety is preferably a therapeutic protein or peptide, preferably insulin or a functional equivalent thereof.

60 Claims, 3 Drawing figures

WEST

Generate Collection Print

L2: Entry 3 of 7 File: USPT Oct 30, 2001

DOCUMENT-IDENTIFIER: US 6309633 B1
TITLE: Amphiphilic drug-oligomer conjugates with hydroyzable lipophile components and methods for making and using the same

CLAIMS:

1. A drug-oligomer conjugate having the following general formula:

D--[(H--S.sub.n)--L.sub.o].sub.p (Formula 11)

wherein

D is a therapeutic drug moiety;

H is a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

L is a lipophilic moiety selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, adamantane and fatty acids;

S is a spacer group selected from the group consisting of sugars, carbohydrates and glycerol;

n is a number from 1 to the maximum number of covalent bonding sites at which S can form a bond with H;

o is a number from 1 to the maximum number of covalent bonding sites at which L can form a bond with S;

p is a number from 1 to the maximum number of covalent bonding sites at which --[(H--Sn)--Lo] can form a bond with D; and

the S--H bond is hydrolyzable.

5. A drug-oligomer conjugate having the following general formula:

D--[(H--S.sub.n --H'.sub.q)--L.sub.o].sub.p (Formula 12)

wherein

D is a therapeutic drug moiety;

H and H' are hydrophilic moieties, individually selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

L is a lipophilic moiety selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, adamantane and fatty acids;

S is a spacer group selected from the group consisting of sugars, carbohydrates and glycerol;

n is a number from 1 to the maximum number of covalent bonding sites at which S can form a bond with H;

q is a number from 1 to the maximum number of covalent bonding sites at which H' can form a bond with S;

o is a number from 1 to the maximum number of covalent bonding sites at which L can form a bond with S;

p is a number from 1 to the maximum number of covalent bonding sites at which --[(H--S.sub.n --H'.sub.q)--L.sub.o] can form a bond with D; and

the H--S bond is hydrolyzable.

9. The drug-oligomer conjugate of claim 5 wherein the H'--L bond is non-hydrolyzable, and wherein the (H--S.sub.n --H'.sub.q)--L.sub.o oligomer comprises an H'--L subunit selected from the group consisting of:

CH.sub.3 (CH.sub.2).sub.n (OC.sub.2 H.sub.4).sub.m OH (Formula 3)

wherein n=3 to 25 and m=1 to 7;

CH.sub.3 (CH.sub.2).sub.n (OC.sub.2 H.sub.4).sub.m OCH.sub.2 CO.sub.2 H (Formula 4)

wherein n=3 to 25 and m=1 to 6;

R--(OC.sub.2 H.sub.4).sub.m CH.sub.2 CO.sub.2 H (Formula 6)

wherein m=0 to 5 and R=cholesterol or adamantane;

CH.sub.3 (CH.sub.2 --CH.dbd.CH).sub.6 (CH.sub.2).sub.2 (OC.sub.2 H.sub.4).sub.m OH (Formula 8)

wherein m=1 to 7; and

CH.sub.3 (CH.sub.2 --CH.dbd.CH).sub.6 (CH.sub.2).sub.2 CX(OC.sub.2 H.sub.4).sub.m OH (Formula 9)

wherein m=1 to 7 and X=NH.

11. A drug-oligomer conjugate having the following general formula:

D--[(H--H'.sub.q --S.sub.n)--L.sub.o].sub.p (Formula 13)

wherein

D is a therapeutic drug moiety;

H and H' are hydrophilic moieties, individually selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

L is a lipophilic moiety selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, and fatty acids;

S is a spacer group selected from the group consisting of sugars, carbohydrates and glycerol;

q is a number from 1 to the maximum number of covalent bonding sites at which H' can form a bond with H;

n is a number from 1 to the maximum number of covalent bonding sites at which S can form a bond with H';

o is a number from 1 to the maximum number of covalent bonding sites at which L can form a bond with S;

p is a number from 1 to the maximum number of covalent bonding sites at which --[(H--H'.sub.q --S.sub.n)--L.sub.o] can form a bond with D; and

the H--S bond is hydrolyzable.

15. A drug-oligomer conjugate having the following general formula:

D--[(H--H'.sub.q)--L.sub.o].sub.p (Formula 10)

wherein

D is a therapeutic drug moiety;

H and H' are hydrophilic moieties, individually selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

L is a lipophilic moiety selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, and fatty acids;

the H--H' bond is hydrolyzable and the H'--L bond is not hydrolyzable;

q is a number from 1 to the maximum number of covalent bonding sites at which H' can form a bond with H;

o is a number from 1 to the maximum number of covalent bonding sites at which L can form a bond with H'; and

p is a number from 1 to the maximum number of covalent bonding sites at which --[(H--H'.sub.q)--L.sub.o] can form a bond with D.

21. A drug-oligomer conjugate having the following general formula: ##STR14##

wherein

D is a therapeutic drug moiety;

H and H' are each a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

the H--L bond(s) are hydrolyzable and the D--L' bond(s), when present, are hydrolysable;

L and L' are each a lipophilic moiety, independently selected from the group consisting of alkyl groups having 2-26 carbon atoms, cholesterol, adamantane and fatty acids;

o is a number from 1 to the maximum number of covalent bonding sites on H; and

m+n+p together have a value of at least one and not exceeding the total number of covalent bonding sites on D for the --H', --L' and --H--L substituents, and wherein m and n are each at least 1.

26. A drug-oligomer conjugate having the following general formula: ##STR15##

wherein

D is a therapeutic drug moiety;

H and H' are each a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

the H--L bond(s) are hydrolyzable and the D--L' bond(s), when present, are hydrolysable;

L and L' are each a lipophilic moiety, independently selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, adamantane and fatty acids:

o is a number from 1 to the maximum number of covalent bonding sites on H;

m+n+p together have a value of at least one and not exceeding the total number of covalent bonding sites on D for the --H', --L' and --H--L substituents, and wherein m and n are each at least 1; and

wherein the D--H and D--H' bonds, when present, are independently selected from the group consisting of carbamate, amide and secondary amine.

28. A drug-oligomer conjugate having the following general formula: ##STR16##

wherein

D is a therapeutic drug moiety;

H and H' are each a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

the H--L bond(s) are hydrolyzable and the D--L' bond(s), when present, are hydrolysable;

L and L' are each a lipophilic moiety, independently selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, adamantane and fatty acids;

o is a number from 1 to the maximum number of covalent bonding sites on H;

m+n+p together have a value of at least one and not exceeding the total number of covalent bonding sites on D for the --H', --L' and --H--L substituents, and wherein m and n are each at least 1; and

wherein the H--L bond is selected from the group consisting of ester and carbonate.

32. A drug-oligomer conjugate having the following general formula: ##STR17##

wherein

D is a therapeutic drug moiety;

H and H' are each a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

the H--L bond(s) are hydrolyzable and the D--L' bond(s), when present, are hydrolysable;

L and L' are each a lipophilic moiety, independently selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, adamantane and fatty acids;

o is a number from 1 to the maximum number of covalent bonding sites on H;

m+n+p together have a value of at least one and not exceeding the total number of covalent bonding sites on D for the --H', --L' and --H--L substituents, and wherein m and n are each at least 1; and

wherein the therapeutic drug moiety has at least one available moiety for conjugation selected from the group consisting of --NH2; --OH and --SH, and wherein at least one of the available moieties is conjugated to the H--L moiety.

35. The drug-oligomer conjugate of claim 32 wherein D is an antigen from an organism or associated with a disease state, selected from the group consisting of adenoviruses; anthrax; Bordetella pertussus; Botulism; bovine rhinotracheitis; Branhamella catarrhalis; canine hepatitis; canine distemper; Chlamydiae; Cholera; coccidiomycosis; cowpox; cytomegalovirus; Dengue fever; dengue toxoplasmosis; Diphtheria; encephalitis; Enterotoxigenic E. coli; Epstein Barr virus; equine encephalitis; equine infectious anemia; equine influenza; equine pneumonia; equine rhinovirus; Escherichia coli; feline leukemia; flavivirus; Globulin; haemophilus influenza type b; Haemophilus influenzae; Haemophilus pertussis; Helicobacter pylon; Hemophilus; hepatitis; hepatitis A; hepatitis B; Hepatitis C; herpes viruses; HIV; HIV- 1 viruses; HIV-2 viruses; HTLV; Influenza; Japanese encephalitis; Klebsiellae species; Legionella pneumophila; leishmania; leprosy; lyme disease; malaria immunogen; measles; meningitis; meningococcal; Meningococcal Polysaccharide Group A; Meningococcal Polysaccharide Group C; mumps; Mumps Virus; mycobacteria; Mycobacterium tuberculosis; Neisseria; Neisseria gonorrhoeae; Neisseria meningitidis; ovine blue tongue; ovine encephalitis; papilloma; parainfluenza; paramyxoviruses; Pertussis; Plague; Pneumococcus; Pneumocystis carinii; Pneumonia; Poliovirus; Proteus species; Pseudomonas aeruginosa; rabies; respiratory syncytial virus; rotavirus; Rubella; Salmonellae; schistosomiasis; Shigellae; simian immunodeficiency virus; Smallpox; Staphylococcus aureus; Staphylococcus species; Streptococcus pneumoniae; Streptococcus pyogenes; Streptococcus species; swine influenza; tetanus; Treponema pallidum; Typhoid; Vaccinia; varicella-zoster virus; and Vibrio cholerae.

38. A drug-oligomer conjugate having the following general formula: ##STR18##

wherein

D is a therapeutic drug moiety;

H and H' are each a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

the H--L bond(s) are hydrolyzable and the D--L' bond(s), when present, are hydrolysable;

L and L' are each a lipophilic moiety, independently selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, adamantane and fatty acids having 4-26 carbon atoms;

o is a number from 1 to the maximum number of covalent bonding sites on H; and

m+n+p together have a value of at least one and not exceeding the total number of covalent bonding sites on D for the --H', --L' and --H--L substituents, and wherein m and n are each at least 1.

40. A drug-oligomer conjugate having the following general formula: ##STR19##

wherein

D is a therapeutic drug moiety;

H and H' are each a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

the H--L bond(s) are hydrolyzable and the D--L' bond(s), when present, are hydrolysable;

L and L' are each a lipophilic moiety, independently selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, adamantane and fatty acids;

o is a number from 1 to the maximum number of covalent bonding sites on H;

m+n+p together have a value of at least one and not exceeding the total number of covalent bonding sites on D for the --H', --L' and --H--L substituents, and wherein m and n are each at least 1; and

wherein H--L is selected from the group consisting of:

CH.sub.3 (CH.sub.2).sub.n CX(OC.sub.2 H.sub.4).sub.m OH (Formula 5)

wherein n=3 to 25, m=1 and X.dbd.O;

R--OCO(C.sub.2 H.sub.4 O).sub.m CH.sub.2 CO.sub.2 H (Formula 7)

wherein m=0 to 5 and R=cholesterol or adamantane; and

CH.sub.3 (CH.sub.2 --CH.dbd.CH).sub.6 (CH.sub.2).sub.2 CX(OC.sub.2 H.sub.4).sub.m OH (Formula 9)

wherein m=1 to 7 and X=O.

45. A method for solubilizing a drug in an oil containing pharmaceutical formulation comprising:

a) providing a drug-oligomer conjugate having a formula: ##STR20##

where

D is a therapeutic drug moiety;

H and H' are each a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

the H--L bond(s) are hydrolyzable and the D--L' bond(s), when present, are hydrolysable;

L and L' are each a lipophilic moiety, independently selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, adamantane and fatty acids;

o is a number from 1 to the maximum number of covalent bonding sites on H,

m+n+p together have a value of at least one and not exceeding the total number of covalent bonding sites on D for the --H', --L' and --H--L substituents, and wherein m and n are each at least 1;

b) bringing the drug-oligomer conjugate of a) into association with an oil containing pharmaceutical formulation.

49. A method for providing a drug-hydrophile conjugate to a situs of a subject, the method comprising administering to the subject a drug-oligomer conjugate having the formula: ##STR21##

wherein

D is a therapeutic drug moiety;

H and H' are each a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

L and L' are each a lipophilic moiety, independently selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, adamantane and fatty acids,

o is a number from 1 to the maximum number of covalent bonding sites on H;

m+n+p together have a value of at least one and not exceeding the total number of covalent bonding sites on D for the --H', --L' and --H--L substituents, and wherein m and n are each at least 1; and

the H--L bond(s) and/or the D--L' bonds are hydrolyzable in the subject to provide the drug-hydrophile conjugate.

56. A method for providing a drug-PEG conjugate to a situs of a subject, wherein the drug component of the drug-PEG conjugate is selected from the group consisting of insulin and functional equivalents of insulin, and wherein the drug-PEG conjugate has enhanced activity in comparison with a corresponding unconjugated insulin molecule, the method comprising administering to the subject a drug-PEG-lipophile conjugate having a formula:

D--[(H--H'.sub.q)--L.sub.o].sub.p (Formula 10)

wherein

D is selected from the group consisting of insulin and functional equivalents of insulin;

H is a straight or branched PEG polymer having from 2 to 7 PEG subunits;

H' is a straight or branched PEG polymer having from 0 to 130 PEG subunits;

L is a lipophilic moiety selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, and fatty acids;

q is a number from 1 to the maximum number of covalent bonding sites at which H' can form a bond with H;

o is a number from 1 to the maximum number of covalent bonding sites at which L can form a bond with H';

p is a number from 1 to the maximum number of covalent bonding sites at which --[(H--H'.sub.q)--L.sub.o] can form a bond with D; and

the H--H' bond is hydrolyzed in the subject to provide the drug-PEG conjugate.

WEST

Generate Collection | Print

L2: Entry 4 of 7 File: USPT Oct 23, 2001

US-PAT-NO: 6306838
DOCUMENT-IDENTIFIER: US 6306838 B1

TITLE: Targeted vesicular constructs for cyto protection and treatment of h. pylori

DATE-ISSUED: October 23, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Singh; Amarjit	New Delhi			IN
Jain; Rajesh	New Delhi			IN

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Panacea Biotec Limited	New Delhi			IN	03

APPL-NO: 09/ 490127 [PALM]
DATE FILED: January 24, 2000

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
IN	141/DEL/99	January 25, 1999

INT-CL: [07] A61 K 31/685, A61 K 31/65, A61 K 31/56

US-CL-ISSUED: 514/78; 514/152, 514/182
US-CL-CURRENT: 514/78; 514/152, 514/182

FIELD-OF-SEARCH: 514/78, 514/182, 514/152

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	5286492	February 1994	Dettmar et al.	424/458

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
676199	October 1995	EP	
WO 95/28929	November 1995	WO	
WO 95/28943	November 1995	WO	
WO 95/31199	November 1995	WO	
WO 96/24341	August 1996	WO	

OTHER PUBLICATIONS

Forman et al., H Pylori and Gastric Cancer, The Lancet, vol. 343, pp. 243-244, Jan. 22, 1994.
S. Carpenter-Green et al., Intercorporation of Acylated Wheat Germ Into Liposomes, Analytical Biochemistry, vol. 135, pp. 151-155, 1983.
A.A. Bogdanov, Jr., Lectin-Bearing Liposomes: Differential Binding to Normal and To Transformed Mouse Fibroblasts, Experimental Cell Research, vol. 181 (1989) 362-374.
J. R. Warren, Unidentified Curved Bacilli on Gastric Epithelium in Active Chronic Gastritis, The Lancet, pp. 1273-1275, Jun. 4, 1983.
B. J. Marshall et al., Unidentified Curved Bacilli in the Stomach of Patients With Gastritis and Peptic Ulceration, The Lancet, Jun. 16, 1984, pp. 1311-1315.
G. E. Buck et al., Relation of Campylobacter Pyloridis to Gastritis and Peptic Ulcer, The Journal of Infectious Diseases, vol. 153, No. 4, Apr. 1986, pp. 664-669.
F. J. Hutchinson et al., Lectin-Mediated Targeting of Liposomes to a Model Surface, FEBS Letters, vol. 234, No. 2, pp. 493-496, Jul. 1988.
D. Y. Graham, Campylobacter Pylori and Peptic Ulcer Disease, Gastroenterology, vol. 96, No. 2, 1989, pp. 615-625.
J. P. Liautard et al, Controlled Binding of Liposomes to Cultured Cells by Means of Lectins, Cell Biology International Reports, vol. 9, No. 12, Dec. 1985, pp. 1123-1137.
M. Kaszuba et al, The Preparation and Characterisation of Proteoliposomes for Targeting to Oral Bacteria, Biochemical Society Transactions, 1991.
C. S. Goodwin et al., Transfer of Campylobacter Pylori and Campylobacter Mustelae to Helicobacter Gen. Nov. As Helicobacter Pylori Comb. Nov. And Helicobacter Mustelae Comb. Nov., Respectively, International Journal of Systematic Bacteriology, Oct. 1989, p. 397-405, vol. 39, No. 4.

ART-UNIT: 164

PRIMARY-EXAMINER: Weddington; Kevin E.

ATTY-AGENT-FIRM: Oblon, Spivak, McClelland, Maier & Neustadt, P.C.

ABSTRACT:

A Novel Composition for targeted vesicular for treatment of H-Pylori infections and for protection of the cell is disclosed. The Composition Comprises Lectins, Phospholipids sterols an one or more drugs. The Composition is useful since not only it treats H-Pylori infections and other diseases associated therewith but also helps in protection of the cell walls.

12 Claims, 3 Drawing figures

WEST Search History

DATE: Monday, August 25, 2003

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT; PLUR=YES; OP=AND		
L1	(cholesterol or dipalmitoyl$ or di-palmitoyl$ or dimyristoyl$ or di-myristoyl$).clm.	3594	L1
L2	L1 and (pylori or pyloris or pyloridis or pylor or pylon or helicobacer or helicobacter or helliobacter or hpylori).clm.	7	L2
L3	lipid.clm. and (pylori or pyloris or pyloridis or pylor or pylon or helicobacer or helicobacter or helliobacter or hpylori).clm. not l2	12	L3
L4	L3 and lewis.clm.	0	L4
L5	t-helper.clm.	34	L5
L6	th1.clm. or th-1.clm.	140	L6
L7	L6 or l5	174	L7
L8	l7 and (pylori or pyloris or pyloridis or pylor or pylon or helicobacer or helicobacter or helliobacter or hpylori).clm. not l2 not l3	0	L8
L9	l7 and (pylori or pyloris or pyloridis or pylor or pylon or helicobacer or helicobacter or helliobacter or hpylori).clm.	0	L9
L10	l7 and (pylori or pyloris or pyloridis or pylor or pylon or helicobacer or helicobacter or helliobacter or hpylori)	2	L10

END OF SEARCH HISTORY

WEST Search History

updated 8/2003 VSP

DATE: Monday, August 25, 2003

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT; PLUR=YES; OP=AND		
L1	dc-chol or d-c-chol or dcchol	218	L1
L2	L1 and (helicobacter or pylori or pyloris or pyloridis or pylorum or hpylori or heliobacter or pylor or pylon or helicobacter)	3	L2
L3	DOTAP or DOTMA or DC-Chol	1183	L3
L4	L3 and (helicobacter or pylori or pyloris or pyloridis or pylorum or hpylori or heliobacter or pylor or pylon or helicobacter)	32	L4
L5	L4 not l2	29	L5
L6	protein near5 (kinasec or kinase-c or (kinase near c))	3755	L6
L7	l6 and (helicobacter or pylori or pyloris or pyloridis or pylorum or hpylori or heliobacter or pylor or pylon or helicobacter)	33	L7

END OF SEARCH HISTORY